Total Synthesis and Revised Structure of Biyouyanagin A

Nicolaou, K. C.; Sarlah, D.; Shaw, D. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 4708.

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Current Literature Presentation
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Biological Significance of Biyouyanagin A

- Isolated from the leaves of *H. Chinense L.* var. *salicifolium*, a Japanese folk medicine (Biyouyanagi) for the treatment of female disorders

- Selective inhibition against HIV replication in H9 lymphocytes (EC_{50} = 0.798 μgml^{-1}) compared with noninfected H9 lymphocytes (EC_{50} > 25 μgmL^{-1})

Anti-HIV Activity of **1**

compd	IC_{50} (μg/mL)	EC_{50} (μg/mL)	TI
biyouyanagin A (**1**)	>25	0.798	31.3
AZT	500	0.0021	238, 738

- Inhibition of lipopolysaccharide (LPS)-induced cytokine production

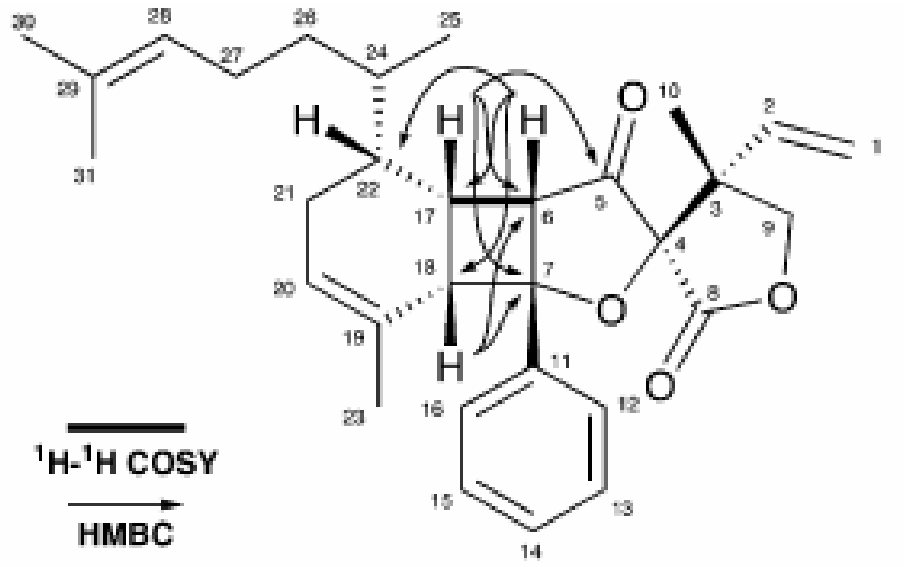
Inhibitory Effects for Cytokine Release of **1**[a]

	cytokine production ratio		
compd	IL-10	IL-12	TNF-α
biyouyanagin A (**1**)	0.03	0.02	0.48
prednisolone	0.14	0.24	0.48

[a] PBMCs were treated with lipopolysaccharide (LPS) in the presence of **1** (10 μg/mL). Prednisolone (0.3 μg/mL) was used as a reference sample. Data were expressed as ratios to cytokine production induced by LPS.

Tanaka, N. et al. *Org. Lett.* **2005**, *7*, 2997-2999.

Initial Proposed Structure of Biyouyanagin A



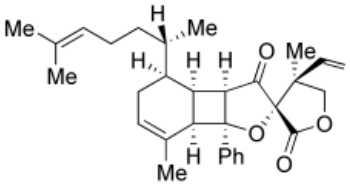
Biyouyanagin A (**1**).

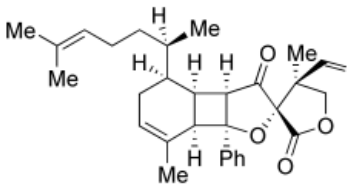
- Structure comprised of sesquiterpene, cyclobutane, and spirolactone moieties

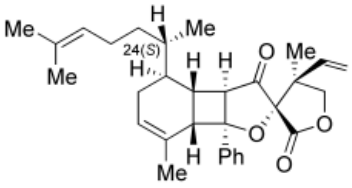
- Relative configuration established from NOE correlations: H-6 with H-17, -22, and aromatic protons; H-17 with H-18, -22; H_3-10 with aromatic protons

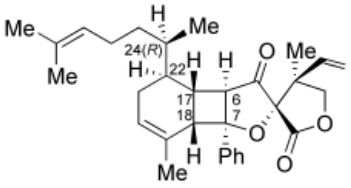
Tanaka, N. et al. *Org. Lett.* **2005**, *7*, 2997-2999.

Retrosynthetic Analysis

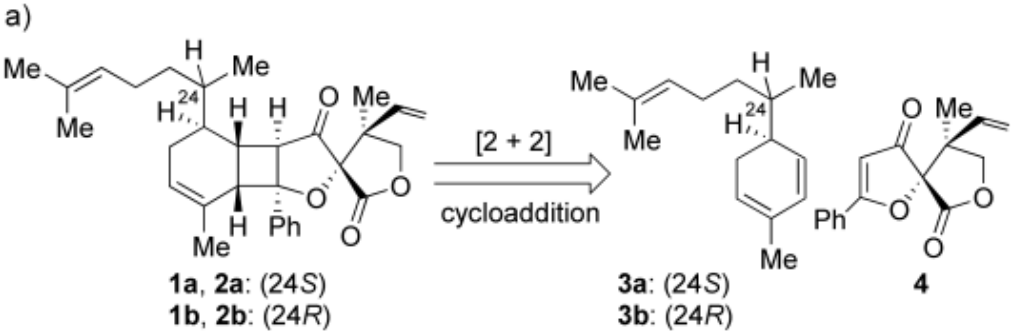


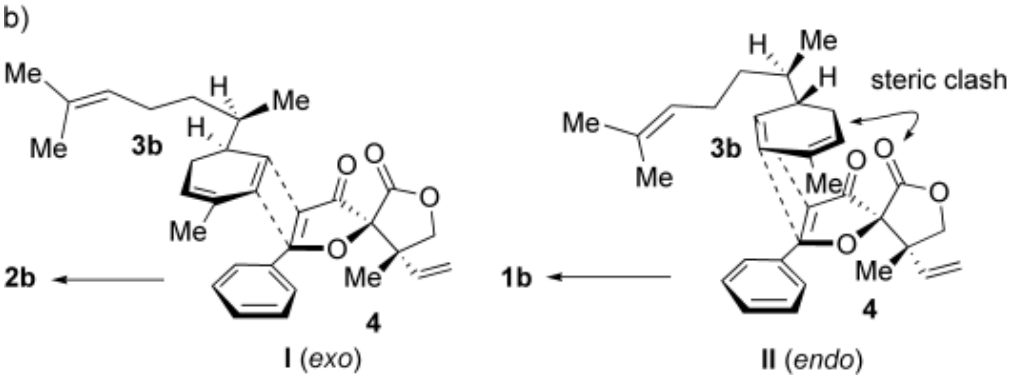






➢ Originally proposed (**1a** and **1b**) and revised (**2a** and **2b**) structures





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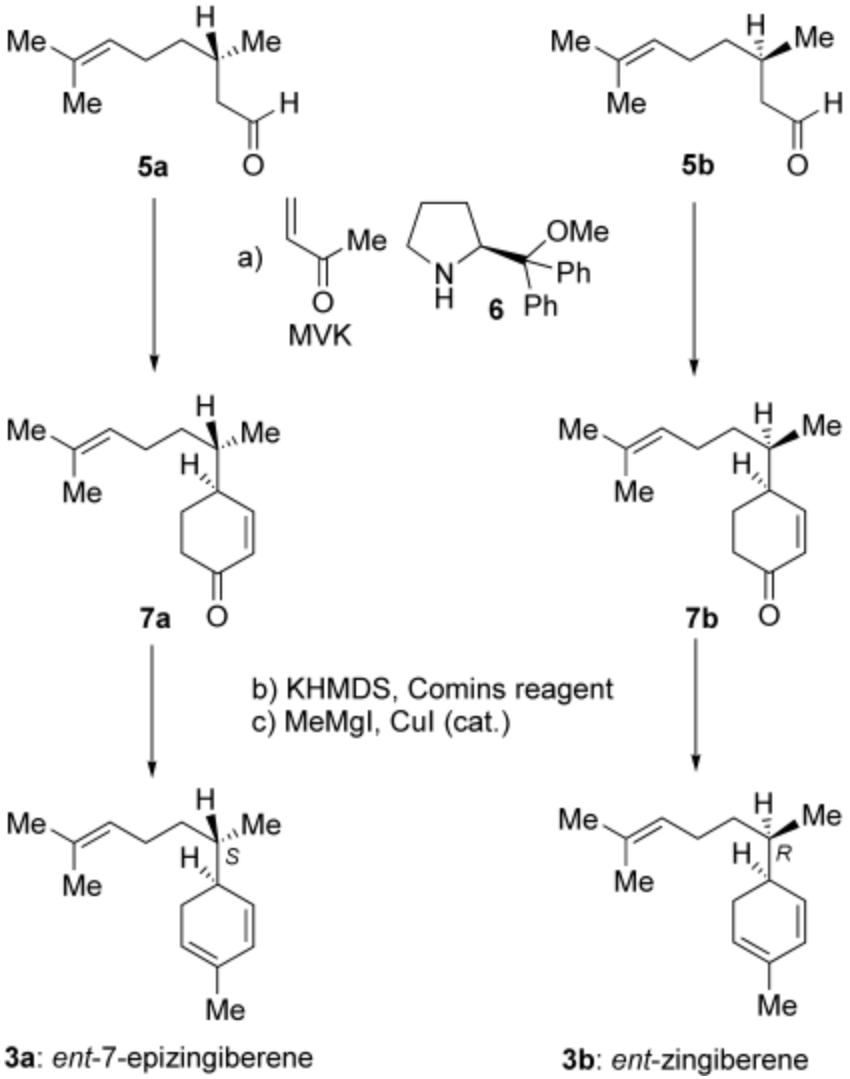
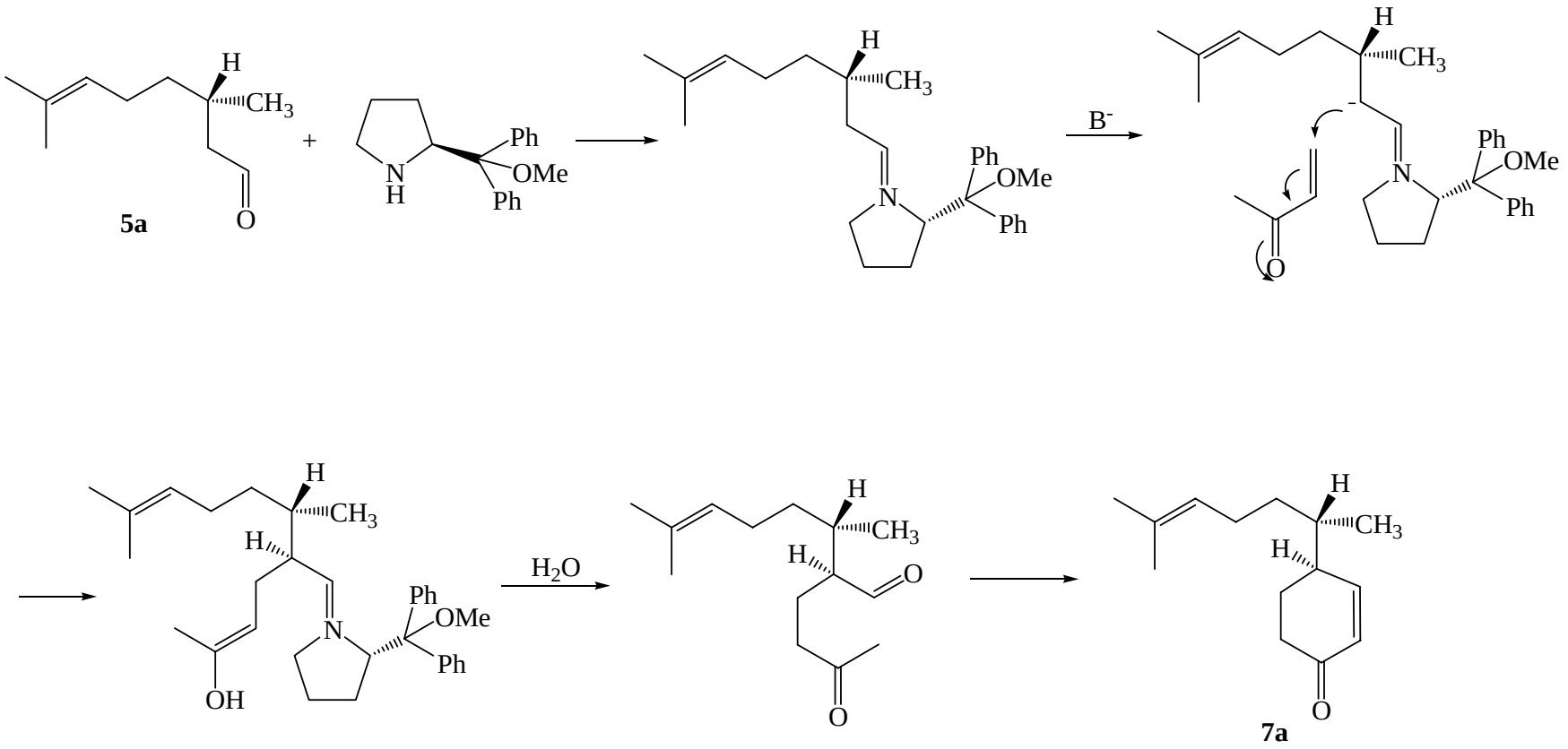
Synthesis of **3a** and **3b**



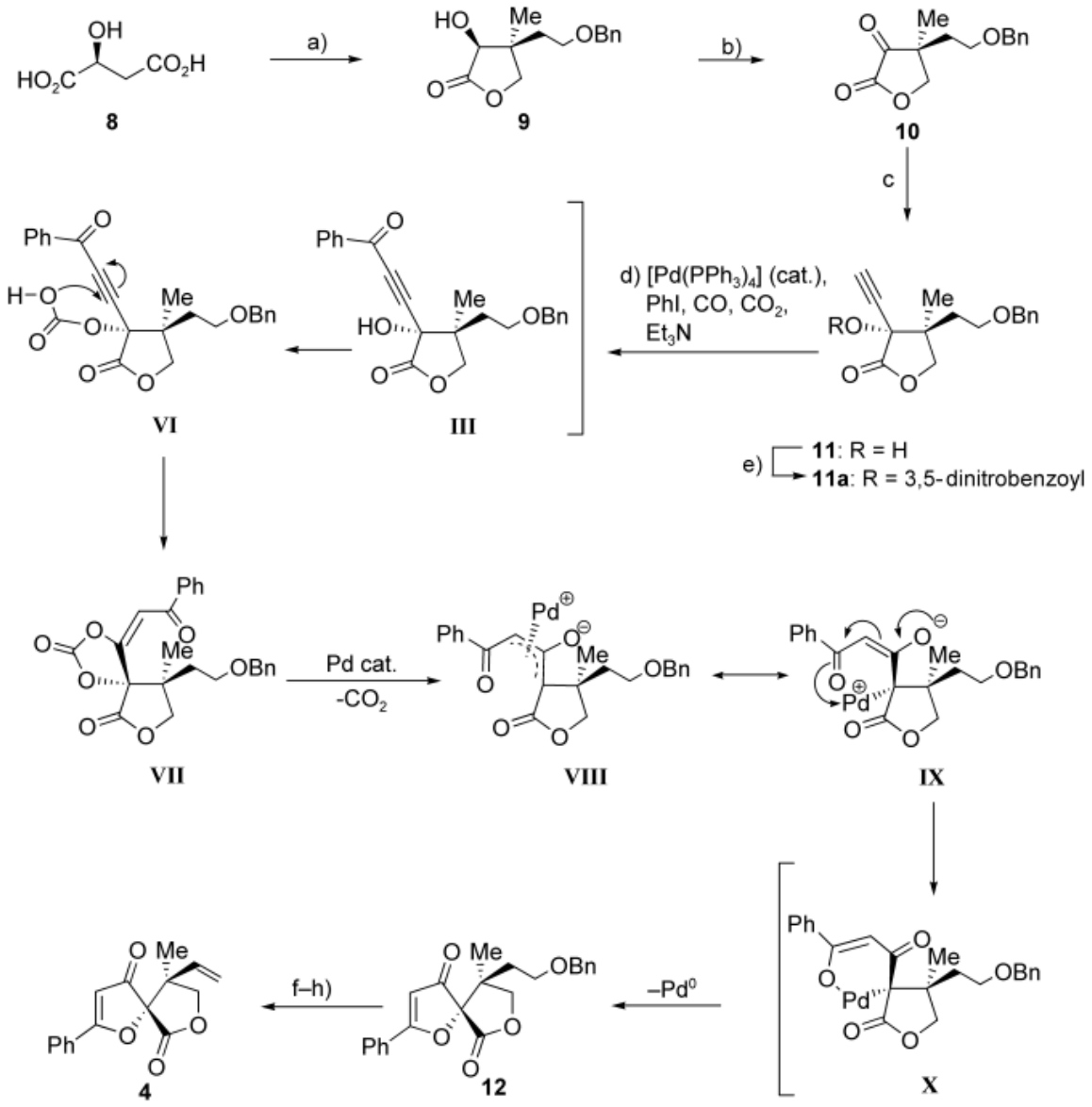
Reagents and conditions: a) **5a** or **5b** (1.0 equiv), MVK (1.5 equiv), **6** (5 mol%), ethyl 3,4-dihydroxybenzoate (20 mol%), 0 °C, 24 h; then KOH (0.1 *N* aq, 1.0 equiv), nBu$_4$NOH (40% aq, cat.), Et$_2$O/THF/H$_2$O (3:1:3), reflux, 6 h, 72% yield, 93% de for **7a**; 68% yield, 86% de for **7b**; b) KHMDS (1.5 equiv), THF, -78 °C, 3 h; then Comins reagent (1.5 equiv), THF, -78 °C, 1 h; c) MeMgI (3.0 M in Et$_2$O, 1.5 equiv), CuI (2 mol%), THF, 0 °C, 15 min, 80% (2 steps).

Michael Addition/Aldol Sequence



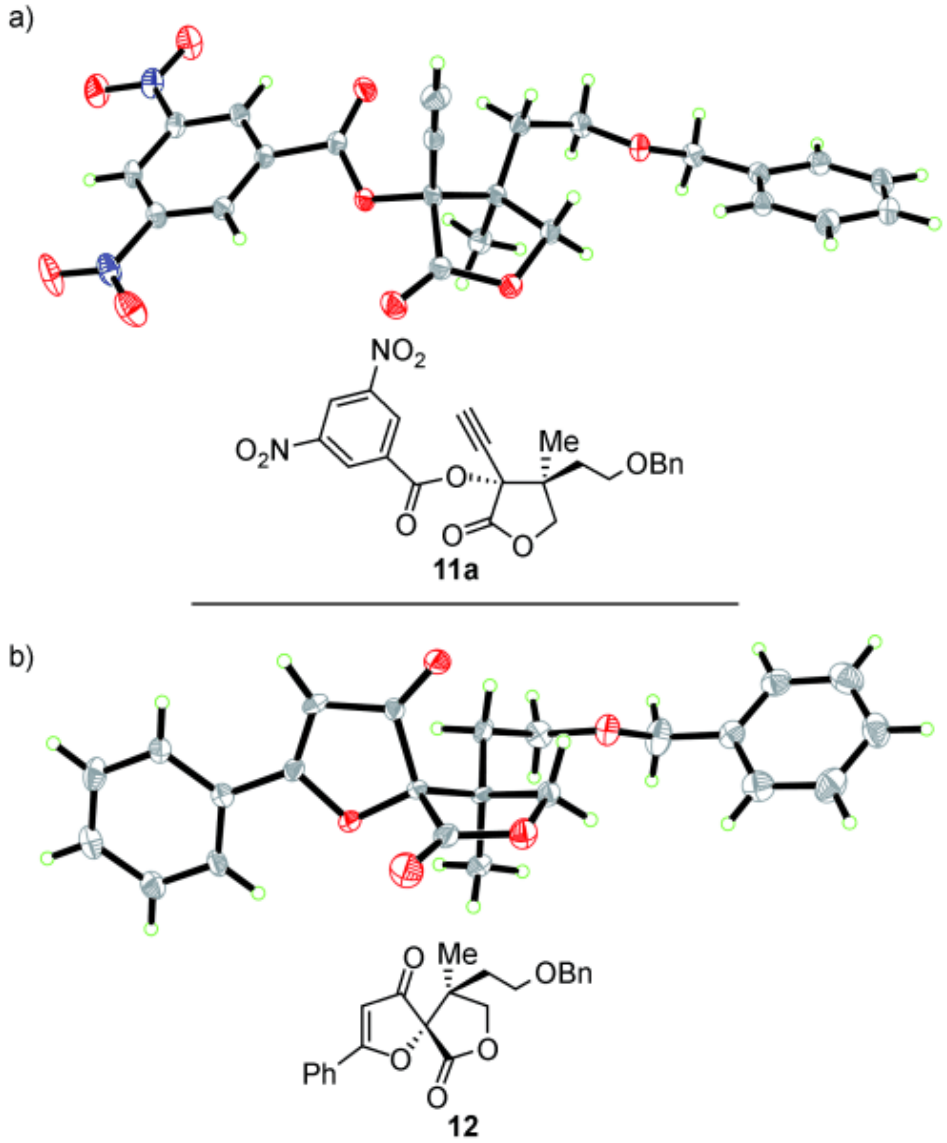
Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253-4256.

Synthesis of hyperolactone C (**4**)

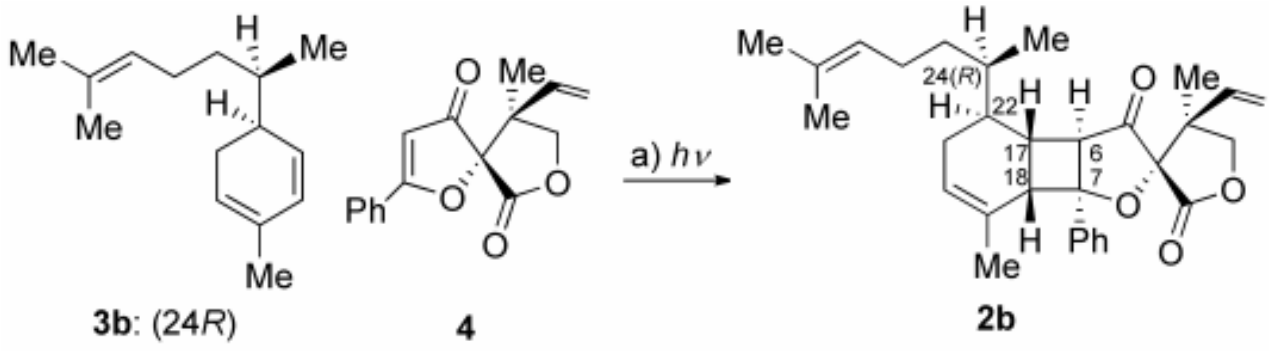


Reagents and conditions: a) Ueki, T. et al. *Tetrahedron Lett.* **1998**, *39*, 667; 20% for three steps; b) DMP (2.0 equiv), CH_2Cl_2, 25 °C, 5 h, 92%; c) acetylene, *n*BuLi, THF, -78 °C, 1 h, 79%, 3:1 d.r.; d) $[Pd(PPh_3)_4]$ (5 mol%), PhI, CO (200 psi), CO_2 (200 psi), Et_3N, 100 °C, 5 h, 77%; e) 3,5-dinitrobenzoyl chloride (1.2 equiv), NEt_3 (1.2 equiv), DMAP (0.1 equiv), CH_2Cl_2, 25 °C, 3 h, 87%; f) BBr_3 (1.5 equiv), CH_2Cl_2, -78 °C, 30 min; g) *o*-NO_2PhSeCN (1.2 equiv), P(*n*Bu)3 (1.2 equiv), THF, 25 °C, 4 h; h) H_2O_2 (30% aq, excess), THF, 25 °C, 1 h, 73% (3 steps).

Retention of Stereochemistry from **11** to **12**

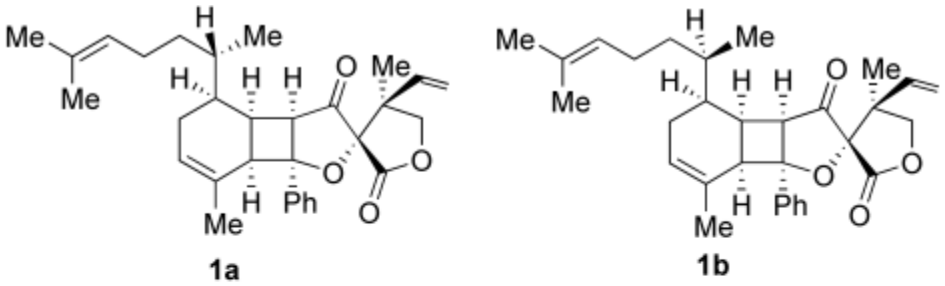


Completion of the Synthesis



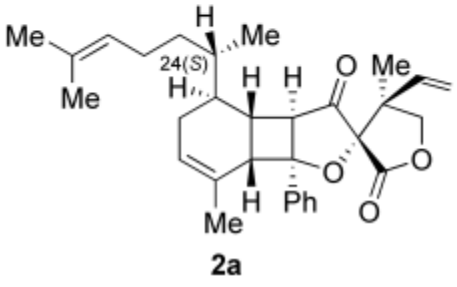
Reagents and conditions: a) **4** (1.0 equiv), **3b** (4.0 equiv), 2'-acetonaphthone (1.0 equiv), CH_2Cl_2, 25 °C, 5 h, 46%.

Interpretation of NMR Data

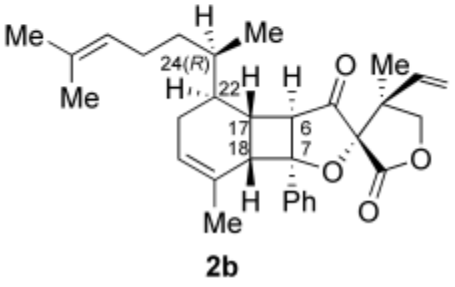


1a

1b



2a



2b

➢ A strong NOE interaction between H6 and aromatic protons (ca. 1:128 ratio, 400 MHz, irradiation) firmly confirms the *cis* relationship between H6 and the phenyl group, whereas the absence of a strong NOE interaction between H18 and aromatic protons eliminates **1a** and **1b**.

➢ It was assumed that the NOE interaction between H6 and H17 is indicative of a syn arrangement, whereas this is not necessarily the case.

Summary

- The first stereoselective synthesis of Biyouyanagin A has been achieved over 12 steps in 3.8% overall yield.
- Stereochemical assignment of the natural product was revised from **1a** or **1b** to **2b**.
- A novel [2+2] photocycloaddition reaction was crucial for the short synthesis of Biyouyanagin A .
- Structural assignment based on NMR analysis alone should be viewed with special caution..